With reference to the experimental results, the present method was applied using the region of amino acid numbers of 289 to 364 as an active site region and operation was attempted (Figure 30). The results are shown in Table 9.

Page 43, first paragraph:

on the kunitz protease inhibitors described in a known literature (P. Ponte et al., Nature, 331, 525-527 (1988)), characteristic frequency value thereof was 0.3281. Among the above 5 values, 0.3203 is the most closest value. Therefore, the inhibitory activity may be expected as a novel biological activity of the region of 650 to 680 in APP of Example 2.

REMARKS

The specification has been amended to correct some minor typographical errors. Accordingly, it is respectfully requested that the foregoing amendments be entered, that the application as so amended receive an examination on the merits, and that the claims as now presented receive an early allowance.

Respectfully submitted,

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Date: 10/04/01

MARKED-UP VERSION

Page 8, second paragraph:

a total nucleotide sequence frequency spectrum obtained by giving EIIP index values to the nucleotide residues of a nucleotide sequence region academically (J.C. Lacey, Chemtracts Biochem. Mol. Biol., 12, 398-418 (1999); V. Kunin, Orig. Life Evol. Biosphere 30, 459-466 (2000)) corresponding to the above amino acid sequence and subjecting the resulting EIIP sequence to DFT; and

Page 25, second paragraph:

Furthermore, on gamma interferon (R. Wetzel et al., Protein Eng., 3, 611-623 [(1987))] (1990)) wherein the protein whose C-terminal region of the amino acid sequence is deleted is known to exhibit almost no antivirus activity, the present inventor has select characteristic frequency values derived from the active site. The amino acid sequence is registered in SWISS-PROT and comprises 166 amino acid residues. The active site is known to be present at 151-154 residues in the amino acid sequence of gamma interferon. However, in order to clarify the object of the present invention, the active site (247±15) predicted by the present inventor using 13 kinds of motifs is adopted (N. Numao et al., Biol. Pharm. Bull., 16, 1160-1163 (1993)).

Page 38, third paragraph:

Biological activity of normal prion protein has hitherto not been reported (S.B. Prusiner, Proc. Natl. Acad. Sci., U.S.A.A, 95, 13363-13383 (1998); D. Westway et al., Proc. Natl. Acad. Sci., U.S.A., 95, 11030-11031 [(1997))] (1998)). The amino acid sequence has already been registered in SWISS-PROT. According to a known literature (G. Forloni et al., Nature, 362, 543-546 (1993)), the neurotoxic activity is known to exist at around amino acid numbers of 106 to 126 of the prion protein. However, there is a counterevidence that the peptide does not exhibit neurotoxic activity when the peptide of

the sequence is treated at 37°C for 30 days in a buffer solution (pH 7.4) (B. Kunz et al., FEBS Lett., 458, 65-68 (1999)). The present inventor has first determined a self-cross-spectrum of the total amino acid sequence frequency spectrum of the prion and a cross-

Page 40, third paragraph:

Among three types of APP, one is a protein comprising 751 amino acids ([A.] P. Ponte et al., Nature, 331, 525-527 (1988)). The amino acid sequence has already

Page 42, third paragraph:

It is already known that the amino acid sequence in the periphery of 291 to 341 is highly homologous to serine protease inhibitor ([A.] P. Ponte et al., Nature, 331, 525-527 (1988)). In fact, the inhibitory activity of this region has already been reported (N. Kitaguchi et al., Nature, 331, 530-532 (1988)), but the inhibitory activity is not high. With reference to the experimental results, the present method was applied using the region of amino acid numbers of 289 to 364 as an active site region and operation was attempted (Figure 30). The results are shown in Table 9.

Page 43, first paragraph:

on the kunitz protease inhibitors described in a known literature ([A.] P. Ponte et al., Nature, 331, 525-527 (1988)), characteristic frequency value thereof was 0.3281. Among the above 5 values, 0.3203 is the most closest value. Therefore, the inhibitory activity may be expected as a novel biological activity of the region of 650 to 680 in APP of Example 2.